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Human Genome Epidemiology (HuGE) Review

The *E-cadherin* Gene Polymorphism $-160C \rightarrow A$ and Cancer Risk: A HuGE Review and Meta-Analysis of 26 Case-Control Studies

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A single nucleotide polymorphism, $-160C \rightarrow A$, has been identified in the promoter region of the *E-cadherin* gene and has been shown to alter its transcriptional activity. To assess susceptibility of $-160A$ allele carriers to seven types of cancers, the authors conducted a comprehensive meta-analysis, up to November 2006, of 26 case-control studies comprising 7,042 cases and 7,011 controls. Pooled odds ratios and 95% confidence intervals were calculated by using the random-effects model. Publication bias, subgroup, and sensitivity analyses were also performed, which showed that $-160A$ allele carriers, compared with noncarriers, had about a 17–19% increased risk of several invasive/metastatic tumors. Analyses of various types of cancers revealed that, in Europeans, the $-160AA$ homozygote was associated with an increased risk of urothelial cancer, carriers of $-160A$ were at increased risk of lung and prostate cancers, and carriers of $-160A$ with gastric cancer were found to suffer a significantly increased risk, whereas their Asian counterparts seemed to be tolerant. No evidence was found that the $-160A$ allele predisposed its carriers to breast, colorectal, or esophageal cancers. These findings indicate that $-160A$ of the *E-cadherin* gene is emerging as a low-penetrance tumor susceptibility allele for the development of gastric, lung, prostate, and urothelial cancers.

E-cadherin; epidemiology; meta-analysis; mutation; neoplasms

Abbreviations: CI, confidence interval; OR, odds ratio.

Editor's note: *This article also appears on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/default.htm).*

GENE

The *E-cadherin* gene, located on chromosome 16 (16q22.1), encodes a transmembrane glycoprotein that mediates intercellular adhesion as well as cell signaling in conjunction with cytoplasmic catenin proteins. E-cadherin as a calcium-dependent intercellular adhesion molecule is highly expressed in normal epithelial cells and well-differentiated cancer cells, but its expression is largely reduced in undifferentiated cancers. The E-cadherin/catenin complex is important for cellular polarity and maintenance of normal tissue morphology and cellular differentiation (1). As a tumor suppressor, defective E-cadherin expression governs transition to an invasive phenotype in human epithelial cancers (2, 3). In addition, disruption of E-cadherin with rare mutations may also be involved in carcinogenesis through a modified Wnt signaling pathway (4).

GENE VARIANT

Recently, a *C/A* single nucleotide polymorphism has been identified in the promoter region of the *E-cadherin* gene

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TABLE 1. Estimates of odds ratios and the corresponding 95% confidence intervals for *AA*, *CA* genotypes and *A* allele carriers versus the *CC* genotype for seven types of cancers analyzed by a random-effects model, up to November 2006

Cancer type	No. of data sets	No. of cases	No. of controls	*AA*		*CA*		(*AA* + *CA*)	
				OR†	95% CI	OR	95% CI	OR	95% CI
Breast	3	1,043	817	1.17	0.83, 1.65	1.11	0.92, 1.35	1.12	0.93, 1.35
Colorectal	3	646	465	0.66	0.12, 3.57	1.24	0.95, 1.63	1.15	0.89, 1.50
Esophageal	2	407	490	1.03	0.27, 3.93	1.30	0.97, 1.73	1.22	0.93, 1.61
Gastric									
Asian	7	1,174	1,279	0.72	0.42, 1.23	0.82	0.64, 1.04	0.81*	0.67, 0.99
European	4	486	536	1.68	0.74, 3.78	1.41*	1.07, 1.85	1.45*	1.06, 1.97
Group total	11	1,660	1,815	1.00	0.62, 1.61	0.98	0.78, 1.23	0.98	0.78, 1.24
Prostate									
Asian	2	455	567	1.64	0.84, 3.21	1.33*	1.01, 1.75	1.36*	1.05, 1.77
European	6	2,178	2,067	1.40	0.82, 2.38	1.31*	1.01, 1.71	1.32*	1.02, 1.70
Group total	8	2,633	2,634	1.43	0.94, 2.19	1.30*	1.07, 1.59	1.31*	1.08, 1.60
Urothelial	3	558	705	2.57*	1.55, 4.24	1.34	0.85, 2.10	1.58	0.95, 2.63
Lung	1	95	85	12.56	0.68, 231.61	2.37*	1.13, 4.99	2.81*	1.36, 5.83
Overall	31	7,042	7,011	1.26	0.98, 1.62	1.17*	1.05, 1.30	1.19*	1.06, 1.33

* Statistically significant, with $p < 0.05$ and a 95% confidence interval (CI) that does not overlap 1.0.
† OR, odds ratio.

−160 base pairs upstream of the transcriptional start site (5). It has been shown that the *A* allele decreased transcriptional efficiency by about 10–68 percent compared with the wild-type *C* allele (5–7). It was also observed that the *C* allele showed much higher binding affinity to transcriptional factor than the mutant allele, indicating that the *−160C/A* variant may alter transcriptional activity of the *E-cadherin* gene and be responsible for decreased E-cadherin expression and increased susceptibility to epithelial cancers.

The frequency of the *−160A* allele varies in different geographic areas and ethnic populations. In Europe, the variant allele frequency ranges from 43.4 percent in Italy to 23.3 percent in the United Kingdom and, in Asia, from a high allele frequency in China (61.0 percent) to a lower frequency in Korea (14.3 percent); there is also marked variation in the frequency of the *−160AA* homozygote from 18.9 percent in Italy to 3.4 percent in the United Kingdom and from 44.0 percent in China to 0 percent in Japan (this information is summarized in Web table 1, the first of two supplementary tables; each is referred to as ''Web table'' in the text and is posted on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/reviews.htm) as well as on the *Journal*'s website (http://aje.oupjournals.org/)). (This paper also includes three supplementary figures, each referred to as ''Web figure'' in the text and posted on the same two websites.) Moreover, genetic effects of the polymorphism have been shown to vary from one type of cancer to the other. Recent epidemiologic studies revealed an increased risk of prostate cancer (8), a protective role for gastric cancer (9), but no significant association with breast cancer (6) or colorectal cancer (10). Otherwise, *−160C/A* has been associated with an increased susceptibility to sporadic diffuse-type gastric cancer (11), but no association with risk of gastric cancer was found (12). Thus, these observations raised quite a controversial question regarding the significance of *−160C/A* in cancer pathogenesis. Obviously, statistical power of an individual study could be very limited for efficient assessment of the *−160A* allele. Integration of these data sets may provide improved statistical power to detect the significance.

DISEASES

This meta-analysis was conducted on seven types of cancers—breast, colorectal, esophageal, gastric, prostate, urothelial, and lung—on the basis of available data sets on the *E-cadherin −160C/A* polymorphism and cancer risk.

Breast cancer is the second leading cause of cancer deaths among women. Established risk factors include age at menarche and first full-term pregnancy, which play a role via hormonal mechanisms (13). In addition to variants in the high-penetrance genes *BRCA1* and *BRCA2*, frequent variants of the *E-cadherin* gene have also been found to raise breast cancer risk (14).

Colorectal cancer is the third most common cause of cancer deaths. A recent study indicates that about 35 percent of all colorectal cancer can be ascribed to inherited genetic susceptibility (15). Expression of E-cadherin has been found to be significantly reduced in colorectal cancer but apparently not as a consequence of allele loss or somatic mutation (16).

Esophageal cancer is one of the most common malignancies. Risk factors include various environmental triggers such as cigarette smoking, alcohol drinking, and malnutrition (17). Genetic susceptibility is also suggested as an important factor in esophageal cancer risk, such as a polymorphism in the promoter region of *E-cadherin* (18).

Gastric cancer is another leading cause of cancer deaths. It is well established that environmental factors such as dietary habits and *Helicobacter pylori* infection are associated with gastric cancer risk (19). Most genetic factors such as single nucleotide polymorphisms in the *E-cadherin* promoter may be critical in gastric carcinogenesis (5, 20).

Prostate cancer is one of the most common cancers among men in developed countries. Established risk factors include age, ethnicity, and family history. In addition, a few low-penetrance susceptibility genes including *E-cadherin* with a higher population frequency may be relevant to prostate cancer risk in combination with environmental factors (21).

Urothelial cancer is the fourth most frequent cancer in men in the United States; exogenous carcinogens are widely recognized as the major cause. Increasing evidence suggests that genetic susceptibility should also be considered as a significant risk factor (22, 23). Furthermore, abnormal expression of E-cadherin might be related to *−160C/A* in urothelial cancer (5).

Lung cancer has remained the leading cause of cancer mortality in the Western world. Although environmental exposures such as cigarette smoking account for most cases, genetic variants as well as gene-environment interactions and epigenetic processes are likely to play a significant role in determining disease susceptibility (24).

To date, there have been 26 known case-control studies in the literature on associating the *E-cadherin −160C/A* polymorphism with different types of cancer in different ethnic populations. The aim of this meta-analysis was to assess the evidence supporting *E-cadherin −160A* as a tumor susceptibility allele by integrating all these case-control studies.

MATERIALS AND METHODS

We conducted a systematic review and meta-analysis in accordance with the guidelines provided by the Human Genome Epidemiology Network (25).

Search strategy

First, we conducted a systematic literature search using the databases MEDLINE (US National Library of Medicine, Bethesda, Maryland) and PubMed (National Center for Biotechnology, National Library of Medicine) before November 2006 with keywords "−160C/A," "rs16260," "polymorphism of the *E-cadherin* gene," or "−160C/A" in combination with "cancer" or "neoplasm" or "carcinoma." The full texts of the candidate articles were examined carefully to determine whether they contained sufficient information on the *−160C/A* polymorphism and cancer risk. Furthermore, reference lists were also reviewed to trace further relevant studies.

Inclusion criteria

The constituent studies for the present meta-analysis were case-control studies with sufficient published data for estimating an odds ratio and corresponding 95 percent confidence interval.

Data extraction

The following information from each study was extracted by two investigators independently: 1) publication data, first author, year of publication, and country of origin; 2) cancer types; 3) study design (hospital based, population based, or nested) and genotyping method; and 4) number of cases and controls with the *CC*, *CA*, and *AA* genotypes. This information is summarized in Web tables 1 and 2.

Meta-analysis

As the first step in the meta-analysis, we tested significance of deviation of genotype distribution at the polymorphic site from that expected from Hardy-Weinberg equilibrium in the control sample for each of the selected case-control data sets. The random-effects model was used to calculate the pooled odds ratio estimates for genotype *AA*, genotype *CA*, and *A*-allele carriers ($AA + CA$) against the *CC* genotype by using review manager version 4.2 software (RevMan; The Cochrane Collaboration, Oxford, England). To evaluate whether results of the data sets were homogeneous, we used Cochran's Q test (26). We also calculated the quantity I^2 that represents the percentage of total variation across studies that is a result of heterogeneity rather than chance (27). As a guide, I^2 values of less than 25 percent may be considered "low," values of about 50 percent may be considered "moderate," and values of more than 75 percent may be considered "high" (27). A value of 0 percent indicates no observed heterogeneity, and larger values show increasing heterogeneity. In the absence of heterogeneity, the random-effects and fixed-effects models will provide similar results. When heterogeneity is significant, both models may be biased (28).

Publication bias was evaluated by using the Begg and Mazumdar adjusted rank correlation test (29) and the Egger regression asymmetry test (30). To evaluate the stability of the results, we performed a one-way sensitivity analysis. The scope of this analysis reflects the influence of an individual data set by estimating the average odds ratio in the absence of each data set (31). Statistical tests performed in the present analysis were considered significant whenever the corresponding null-hypothesis probability was $p < 0.05$.

META-ANALYSIS RESULTS

A total of 31 published studies relevant to the current study were carefully examined, and six of these candidate studies were removed from consideration, the one that reported discovery of the *−160C/A* polymorphism of the *E-cadherin* gene (5) and another five that were not case-control studies (32–36). Web figure 1 illustrates the search strategy for constituent studies in the present meta-analysis. Finally, we used 26 independent case-control studies (6–12, 37–54), including our unpublished data collected on non-small-cell lung cancer. The present study involved a total of 7,042 cases and 7,011 controls.

Overall data analysis

For all 31 data sets extracted from the 26 case-control studies, *−160A* allelic frequency in the pooled cases was

TABLE 2. Heterogeneity test for studies of each genotype in different cancer types (up to November 2006) with Cochran's *Q* test and the quantity I^2, and publication bias test with the Begg and Mazumdar adjusted rank correlation test and the Egger regression asymmetry test

Cancer type	*AA*			*CA*			(*AA* + *CA*)			No. of data sets
	Q value	*p* value	I^2 (%)	*Q* value	*p* value	I^2 (%)	*Q* value	*p* value	I^2 (%)	
Breast	1.49	0.47	0	0.40	0.82	0	0.38	0.83	0	3
Colorectal	5.00	0.08	60.0	0.08	0.96	0	0.65	0.72	0	3
Esophageal	3.20	0.07	68.8	0.03	0.86	0	0.46	0.50	0	2
Gastric										
Asian	10.01	0.12	40.0	10.35	0.11	42.0	7.61	0.27	21.1	7
European	7.09	0.07	57.7	1.67	0.64	0	3.76	0.29	20.1	4
Group total	21.94	0.02	54.4	21.67	0.02	53.8	23.21	0.01	56.9	11
Prostate										
Asian	0.00	0.99	0	0.04	0.84	0	0.04	0.83	0	2
European	17.86	0.003	72.0	16.44	0.006	69.6	17.35	0.004	71.2	6
Group total	18.54	0.01	62.3	16.78	0.02	58.3	17.93	0.01	61.0	8
Urothelial	2.30	0.32	13.2	5.23	0.07	61.7	7.52	0.02	73.4	3
Lung										1
Overall	73.55	<0.0001	59.2	55.56	0.003	46.0	66.06	0.0002	54.6	31
Publication bias tests										
Begg and Mazumdar's *p*		0.30			0.49			0.27		31
Egger's *p*		0.26			0.26			0.13		31

significantly higher than that in the corresponding controls ($Z = 4.4733$, $p = 0.0000077$). The pooled odds ratio estimate was 1.19 (95 percent confidence interval (CI): 1.06, 1.33) (table 1), suggesting that carriers of the *−160A* allele would have a significantly higher risk of being predisposed to developing cancer ($p = 0.002$, Web figure 2). However, genotype distribution in controls from four studies (39, 41, 50, 53) and one group of controls from the study by Jonsson et al. (48) significantly deviated from the expected Hardy-Weinberg equilibrium ($p < 0.05$). After these data sets were excluded, the odds ratio estimate for carriers of the *−160A* allele was 1.22 (95 percent CI: 1.10, 1.35) and $p = 0.0001$, indicating that the risk estimate for the *−160A* carriers to be predisposed to cancer remained almost unchanged before and after excluding the data sets.

Both Cochran's Q test ($Q = 66.06$ with 30 df, $p = 0.0002$) and the estimate of I^2 (54.6 percent) revealed a significant heterogeneity among the constituent studies. To assess the cause of heterogeneity, we carried out subgroup analyses for each type of cancer and ethnic group. Table 1 summarizes the odds ratio estimates for three genotypes at the *−160C/A* site and the corresponding 95 percent confidence intervals for seven types of cancer, and for ethnic groups whenever there were at least two data sets for either of the ethnic groups. The p values for the Begg and Mazumdar test and the Egger test were 0.27 and 0.13, respectively, for the *−160A* allele carriers (table 2), both suggesting a negligible publication bias. Table 2 also illustrates the significance tests for genetic heterogeneity in addition to the publication bias analysis. Furthermore, we performed a one-way sensitivity analysis by removing one data set at a time, and stability of the odds ratio estimates was confirmed (figure 1 and Web figure 3). The analyses for each type of cancer are detailed in the following seven sections of the text.

Breast cancer

Three data sets from two case-control studies (6, 37) were for breast cancer, including 1,043 patients and 817 controls (Web table 1). The heterogeneity test for the pooled data sets was not significant ($Q = 0.38$ with 2 df, $p = 0.83$; $I^2 = 0$ percent), suggesting robustness of the meta-analysis for this cancer type (table 2). In addition, genotypic distributions among all controls were in agreement with the Hardy-Weinberg equilibrium, and we found no significant difference between different ethnic populations. The pooled odds ratio estimate for the *−160A* carriers was 1.12 (95 percent CI: 0.93, 1.35) (Web figure 2). There was no significant difference in either allelic frequency or genotypic frequency between the controls and the breast cancer cases, suggesting that the *−160A* allele conferred no detectable risk of breast cancer.

Colorectal cancer

Three studies investigated susceptibility of *−160A* carriers to colorectal cancer, comprising 646 patients and 465 normal controls (7, 10, 38). When these data sets were analyzed together, there was no significant heterogeneity ($Q = 0.65$ with 2 df, $p = 0.72$; $I^2 = 0$ percent). The odds ratio for the risk of cancer for the *−160A* carriers was estimated as 1.15 (95 percent CI: 0.89, 1.50), which showed no

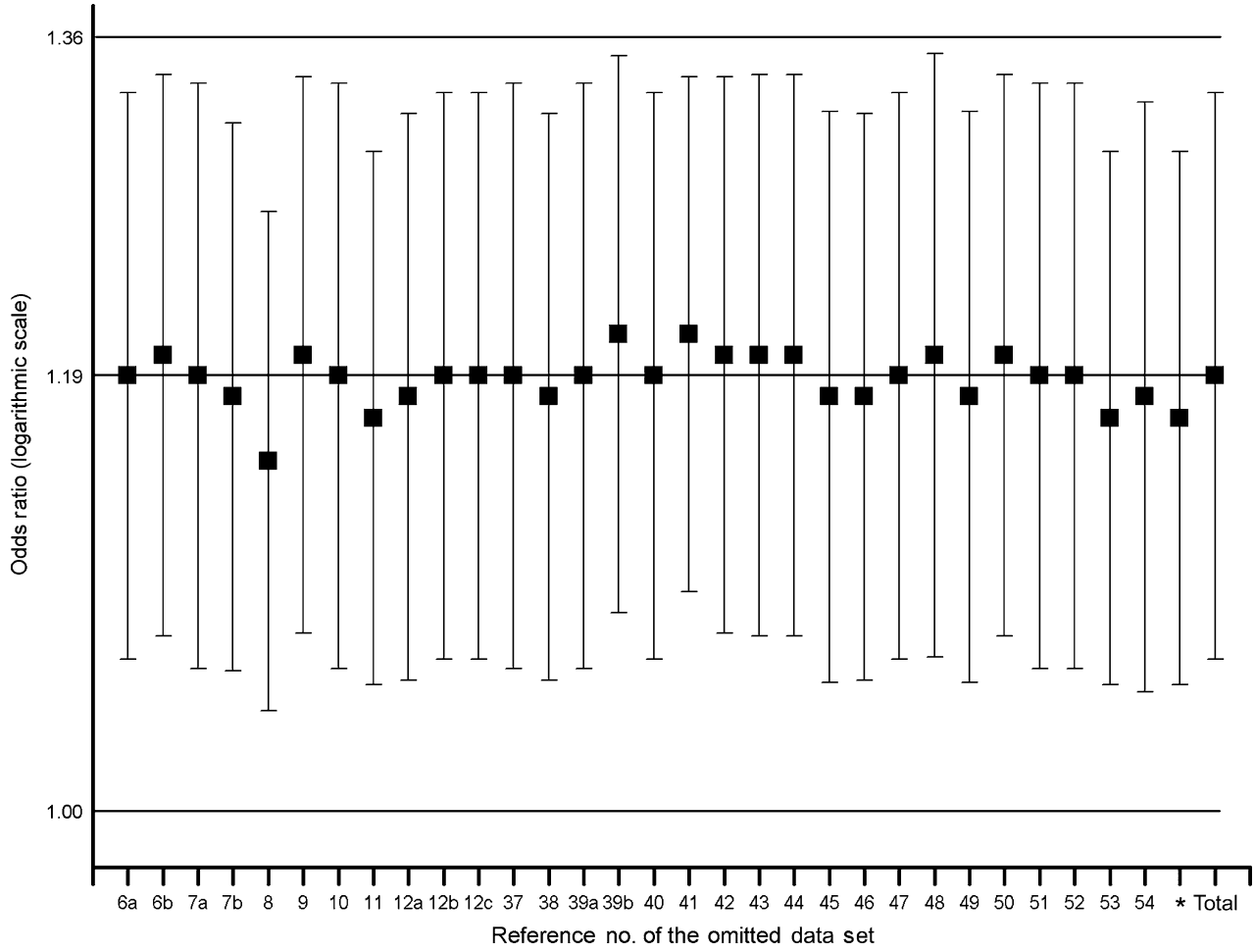

FIGURE 1. One-way sensitivity analysis of the pooled odds ratios and 95% confidence intervals for carriers of the *−160A* allele versus the *CC* genotype, omitting each data set in the meta-analysis (up to November 2006). The pooled odds ratios were calculated by means of a random-effects model. The numbers on the *x*-axis refer to the data sets extracted from referred studies. For instance, 6a indicates the first data set from reference 6. *, the authors' unpublished data set; total, no data set omitted.

significant association of the *−160A* allele with progression of colorectal cancer.

Esophageal cancer

Two studies involving 407 patients and 490 controls detected the *−160C/A* polymorphism in esophageal cancer patients in Japan (7) and China (39). The heterogeneity tests were not statistically significant ($Q = 0.46$ with 1 df, $p = 0.50$; $I^2 = 0$ percent (table 2)). The odds ratio estimate from the pooled data sets for the *−160A* carriers was 1.22 (95 percent CI: 0.93, 1.61) (Web figure 2). No significant difference was detected in allelic and genotypic frequency distribution between patients and controls, implying that the *−160A* allele carriers had no detectable risk of esophageal cancer.

Gastric cancer

Eleven data sets from nine studies were on the *−160C/A* polymorphism and gastric cancer (9, 11, 12, 39–44), which involved 1,660 cases and 1,815 controls. The odds ratio estimate for the *−160A* allele carriers was not significant (odds ratio (OR) = 0.98, 95 percent CI: 0.78, 1.24). However, heterogeneity among these data sets was significant ($Q = 23.217$ with 10 df, $p = 0.01$; $I^2 = 56.9$ percent). Thus, we analyzed Asian and European subgroups separately. In the subgroups, the heterogeneity decreased effectively (table 2). Interestingly, the odds ratio estimates for the *−160A* carriers were less than 1.0 for Asians (OR = 0.81, 95 percent CI: 0.67, 0.99) but significantly greater than 1.0 for Europeans (OR = 1.45, 95 percent CI: 1.06, 1.97) (table 1). This finding demonstrates that the *−160A* allele is an ethnicity-dependent risk factor for gastric cancer.

Prostate cancer

Eight studies focused on the association between the *−160A* allele and prostate cancer, with 2,633 patients and 2,634 controls (8, 45–51). Overall meta-analysis showed

that the *−160A* allele carriers had a significantly increased risk of developing prostate cancer (OR = 1.31, 95 percent CI: 1.08, 1.60). The pooled odds ratio estimates for *−160A* homozygotes and heterozygotes were 1.43 (95 percent CI: 0.94, 2.19) and 1.30 (95 percent CI: 1.07, 1.59), respectively (table 1). However, statistical tests showed a significant heterogeneity among these studies ($Q = 17.93$ with 7 df, $p = 0.01$; $I^2 = 61.0$ percent). To avoid influence of the genetic heterogeneity on the association analysis, we separated the meta-analysis according to Asian and European groups (table 1). The odds ratio estimates for *−160A* allele carriers were 1.36 (95 percent CI: 1.05, 1.77) for Asians and 1.32 (95 percent CI: 1.02, 1.70) for Europeans. However, heterogeneity in the European group was still highly significant ($p < 0.01$). This finding might be mainly attributed to the data set from Verhage et al. (8), in which subjects with benign prostatic hyperplasia, vasectomy patients, and visitors were treated as normal controls. The heterogeneity was effectively removed after exclusion of this data set ($Q = 4.25$ with 6 df, $p = 0.64$; $I^2 = 0$ percent). Sensitivity analysis did not detect significant change in the pooled odds ratio estimates before or after excluding this data set. Overall analysis suggests that *E-cadherin −160A* carriers have an increased risk of prostate cancer.

Urothelial cancer

Three studies investigated predisposition to urothelial cancer for carriers of the *−160C/A* polymorphism, involving 558 patients and 705 controls (52–54). Although no significant association was detected between this polymorphism and various developmental stages of cancer (poorly differentiated and invasiveness), carriers of the *−160AA* genotype had a 2.57-fold increased cancer risk (95 percent CI: 1.55, 4.24) compared with those with the wild-type homozygote. Moreover, a much larger and significant odds ratio estimate (OR = 4.16, 95 percent CI: 1.74, 9.94) was observed for the *−160A* allele carriers in the Chinese study (53). Frequency of the *−160A* allele was significantly higher among invasive than superficial cancer patients, suggesting that *−160C/A* may serve as a prognostic marker for transitional cell carcinoma of the bladder.

Lung cancer

We recently detected the *−160C/A* polymorphism in 95 hospital-based tissue samples from non-small-cell lung cancer cases and 85 randomly selected, normal controls. No occurrence of the *−160A* homozygote was detected in the controls, but five cases were found to carry the *−160AA* genotype. The odds ratio estimate for the *−160A* allele carriers was 2.81 (95 percent CI: 1.36, 5.83), supporting it as a significant susceptibility factor for lung cancer (unpublished data).

DISCUSSION

To our knowledge, the present article is the first general overview of associations between the *E-cadherin −160C/A* polymorphism and susceptibility to seven different types of cancer based on 26 up-to-date case-control studies for which information was available. In the future, this meta-analysis will be updated as evidence emerges.

Our meta-analysis showed that carriers of the *−160C/A* polymorphism had an increased risk of prostate cancer, but there was no obvious difference between Asians and Europeans. In particular, compared with that for the *C* allele in prostate cell lines, transcriptional activity in the *−160A* allele was found to be decreased by 68 percent (5, 45). This evidence is probably the most direct supporting gene functional alteration attributable to the *−160A* carried promoter in prostate cancer.

Although there was no significant association of the *−160A* allele with gastric cancer risk, it conferred a significantly higher risk for Europeans (OR = 1.45) and a tolerant contribution to susceptibility for Asians (OR = 0.81). When compared with their Chinese neighbors, Japanese carriers of the mutant allele even had a decreased risk of gastric cancer (41). In addition, no significant impact of the *−160A* allele on tumor stage and lymph node metastasis was observed. These findings suggest that the *−160A* allele may be a marker for genetic susceptibility rather than a prognostic marker for gastric cancer.

Furthermore, the *−160AA* homozygote conferred a significantly increased urothelial cancer risk (OR = 2.57), and our unpublished data support the *−160A* allele as a significant susceptibility factor for lung cancer. Otherwise, Lin et al. (36) reported a significant 32 percent reduction in recurrence risk for the subjects carrying at least one *−160A* allele, supporting the *−160C/A* polymorphism as a reference molecular marker for urothelial cancer recurrence.

The *−160A* mutant allele was not found to be a statistically significant risk factor for breast, colorectal, or esophageal cancer in this meta-analysis. For breast cancer, the explanation may be that transcriptional activity of the *−160A* allele was reduced by only about 10 percent (6). Regarding colorectal cancer, the *−160C/A* polymorphism showed neither a detectable effect on expression of E-cadherin (7) nor any significant association with localization (10) and microsatellite instability (38), one of the most distinct characteristics of colorectal cancer (55). Otherwise, the study carried out in China did not reveal any association of this polymorphism with lymph node metastasis status (39), but 71 percent of Japanese esophageal cancer patients with the *−160AA* genotype had an invasive phenotype (7). Thus, further research is needed to clarify this inconsistency.

One of the major concerns in a robust meta-analysis is potential bias due to selected publication of the constituent studies, as pointed out by Kaklamani et al. (56). To assess this problem, we presented the relation between the odds ratio estimates in a logarithmic scale and their corresponding standard errors across all constituent data sets and showed that the likelihood of important publication bias in the present analysis was negligible. In fact, both the Begg and Mazumdar adjusted rank correlation analysis and the Egger regression asymmetry test revealed no correlation between the estimate of odds ratio and sample size (table 2).

Another crucial question for any meta-analysis is heterogeneity between the component studies. Lack of proper

consideration of this commonly occurring problem may cause a misleading statistical inference. To test the significance of heterogeneity, we carried out Cochran's Q test and calculated the quantity I^2 that describes the magnitude of heterogeneity across the constituent studies. These analyses are the most popularly recommended in many meta-analyses but could be questionable because statistical power depends heavily on the sample sizes of the component data sets to be pooled (57). Given that the sample sizes used in the gastric cancer case-control studies were moderate in comparison to those in the case and control data sets for other types of cancers, and that significant heterogeneity was detected properly, the statistical tests must be recognized efficiently enough so that the confounder effect of heterogeneity is appropriately detected and assessed for other types of cancer.

The case and control samples in the constituent studies included in the present meta-analysis may have different degrees of selection bias regarding their representativeness of the corresponding natural populations, which could prevent inference from the sample-based analyses to the general population. To minimize potential artifacts in determining entry of research subjects, we conducted the meta-analysis after testing the genotype distribution at the polymorphic site in the control samples. Although there were four data sets in which the genotype distribution did not follow Hardy-Weinberg equilibrium, the corresponding meta-analysis was qualitatively similar with or without excluding them. This finding may indicate that the samples effectively maintained the most important inherent nature of population genetic structure and thus largely improves the predictability and reliability of the meta-analysis. On the other hand, stability of the analysis was confirmed by the sensitivity analysis.

In summary, the present analysis supports growing evidence that *−160A* in the promoter region of the *E-cadherin* gene is emerging as a low-penetrance tumor susceptibility allele in the development of certain forms of cancers such as gastric, lung, prostate, and urothelial. Therefore, this evidence raises the need for exploration of the molecular etiology by which development/progression of cancers can be explained by functional alteration of the *E-cadherin* gene and also the need for investigating this polymorphism as a potential genetic factor for different types of cancer in different ethnic populations.

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